

REMARKS

Claims 1-71 are pending. Claims 1, 21 and 41 are independent claims.
Accompanying this Amendment is a 132 Declaration by Dr. Iwao Ojima.

Rejection under 35 U.S.C. §112 (second paragraph)

Claims 1-71 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the examiner alleges that the taxoid compounds are not clearly defined. (See Office Action page 2, 1st paragraph.)

Claims 1-5, 7-17, 21, 23-37, 41 and 43-57 have been amended to include the structures of the claimed taxoids. Thus, the rejection is obviated.

Applicant has also taken this opportunity to remedy a typographical error in Claims 7-17. In particular, “conjugated” has been replaced with –conjugate--.

Rejection under 35 U.S.C. §102

Claims 1-71 are rejected as allegedly being anticipated by U.S. 5,795,909 to Shashoua et al. (hereinafter “*Shashoua*”). In particular, the examiner contends that *Shashoua* discloses “conjugates of cis-docosahexanoic acid (omega-3 fatty acid) and taxanes used to treat cell proliferative disorders.” The examiner specifically refers to Claim 7 of *Shashoua*. (See Office Action page 2, last paragraph.)

Shashoua relates exclusively to conjugates of first generation taxoids and DHA. In contrast, the pending claims recite conjugates of second generation taxoids and omega-3 fatty acids. In fact, the pending claims are Jepson claims indicating that conjugates of a first generation taxoid and an omega-3 fatty acid are known in the art.

The second generation taxoids substantially differ in structure from the first generation taxoids. In particular, compared to the first generation taxoids, second generation taxoids have modifications at the C-10 and C-3' positions. For example, the C10 position in second generation taxoids is modified with acyl groups; and the phenyl group at the C3'

position is replaced with alkenyl or alkyl groups. To more clearly define the claims, the structure of the second generation taxoids have been added to the independent claims (i.e., Claims 1, 21 and 41).

Thus, *Shashoua* does not disclose the structures recited in the pending claims. Since *Shashoua* does not disclose all the limitations of the pending claims, the pending claims are not anticipated by *Shashoua*. Accordingly, applicant respectfully requests that the anticipation rejection be withdrawn.

Rejection under 35 U.S.C. §103

Claims 1-71 are rejected as allegedly being obvious in view of *Shashoua*. (See Office Action pages 3 and 4.)

As described in the above anticipation rejection, *Shashoua* relates exclusively to first generation taxoid (FGT)-DHA conjugates; whereas, the pending claims recite second generation taxoids (SGT)-omega-3 fatty acid conjugates. Since *Shashoua* does not disclose all the limitations of the pending claims (i.e., does not disclose SGT), the pending claims cannot be obvious over *Shashoua*. Accordingly, applicant respectfully requests that the rejection be withdrawn.

Nevertheless the applicant would like to further address the examiner's following statement appearing in the 1st paragraph on page 4 of the Office Action:

Omega-3 fatty acids are known to be combinable with taxanes to produce conjugates; and taxanes are known to treat cell proliferation. Replacement of a compound with another compound belonging to the same class...is well within the ordinary skill of one in the art as the results, combining a taxane and an omega-3 fatty acid to arrive at a conjugate, would not have been unexpected.

It is critical to note that *Shashoua* simply discloses *in vitro* cytotoxicity evaluations of its conjugates. Due to the known unpredictability of *in vitro* results, a skilled artisan would have believed that the *in vivo* efficacy of FGT-DHA-conjugates could not have been predicted from such *in vitro* cytotoxicity evaluations. See paragraph 3 of Dr. Ojima's accompanying declaration. Thus, a skilled artisan considering *Shashoua* at the time of the present invention would not have attributed much weight to the *in vitro* evaluations.

The instant specification presents *in vivo* experimental results of SGT-DHA conjugates compared with the FGT-DHA conjugates of *Shashoua*. In particular, the antitumor activity against the drug-resistant human colon tumor xenograft (pgp+) DLD-1 and the drug sensitive human ovarian tumor xenograft (pgp-) A121 in SCID mice was evaluated. See Example 13, Tables 1 and 2, and Figures 1 and 2 of the specification. The results show that SGT conjugates have an unexpectedly much greater anti-tumor effect than FGT conjugates. DHA-SBT-1214 and DHA-SBT-1213 were shown to be particularly effective for the drug-resistant human colon tumor xenograft. In contrast, the FGT conjugate (i.e., DHA-paclitaxel) was “totally ineffective” for such colon tumor xenograft.

Dr. Ojima’s accompanying declaration provides further *in vivo* results. In paragraph 5 of the declaration, an experiment is described that compared the efficacy of the SGT-DHA-conjugate (i.e., DHA-SBT-1214) with DHA-paclitaxel against the H460 human lung tumor xenograft implanted s.c. in SCID female mice. DHA-SBT-1214 resulted in significant tumor growth delays or regression/eradication as compared to DHA-paclitaxel. Dr. Ojima concludes, “The results unambiguously demonstrate the distinct superiority of the second-generation DHA-taxane conjugate to the first generation DHA-taxane conjugate, DHA-paclitaxel.”

In paragraph 6 of his declaration, Dr. Ojima describes an experiment in which he compared the *in vivo* efficacy of DHA-SB-T-1214 with that of paclitaxel against the PANC-1 human pancreatic tumor xenograft in SCID mice. Again, DHA-SB-T-1214 shows superior results.

In paragraph 7 of his declaration, Dr. Ojima describes his investigation of another omega-3 fatty conjugate. In particular, Dr. Ojima investigated the efficacy of a SGT conjugate composed of the α -linolenic acid (LNA) and SB-T-1214 against DLD-1 colon tumor xenograft (pgp+). Again, DHA-SB-T-1214 shows highly effective results.

Thus, omega-3 fatty acid-SGT conjugates show unexpectedly better results *vis-à-vis* the DHA-FGT conjugates of *Shashoua*. Such results could not have been reasonably expected or predicted from the *in vitro* results disclosed in *Shashoua*. Thus, applicant respectfully request withdrawal of the obviousness rejection.

Applicant: Iwao Ojima
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Applicant respectfully submits that the application is in all respects complete and in condition for allowance. If the examiner has any questions or comments, it is respectfully requested that the examiner contact applicant's undersigned attorney at the telephone number provided below.

Respectfully submitted,

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